CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211527Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 1, 2019
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	NDA 211527
Product Name and Strength:	Aklief (trifarotene) cream, 0.005%
Applicant/Sponsor Name:	Galderma Research and Development, LLC
FDA Received Date:	August 30, 2019 and September 13, 2019
OSE RCM #:	2018-2153-2
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised 30 gram container label, Prescribing Information (PI) and Patient Package Insert (PPI) received on August 30, 2019 and revised container labels and carton labeling on September 13, 2019 for Aklief. Division of Dermatology and Dental Products (DDDP) requested that we review the revised container labels, carton labeling, Prescribing Information (PI), and Patient Package Insert (PPI) for Aklief (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

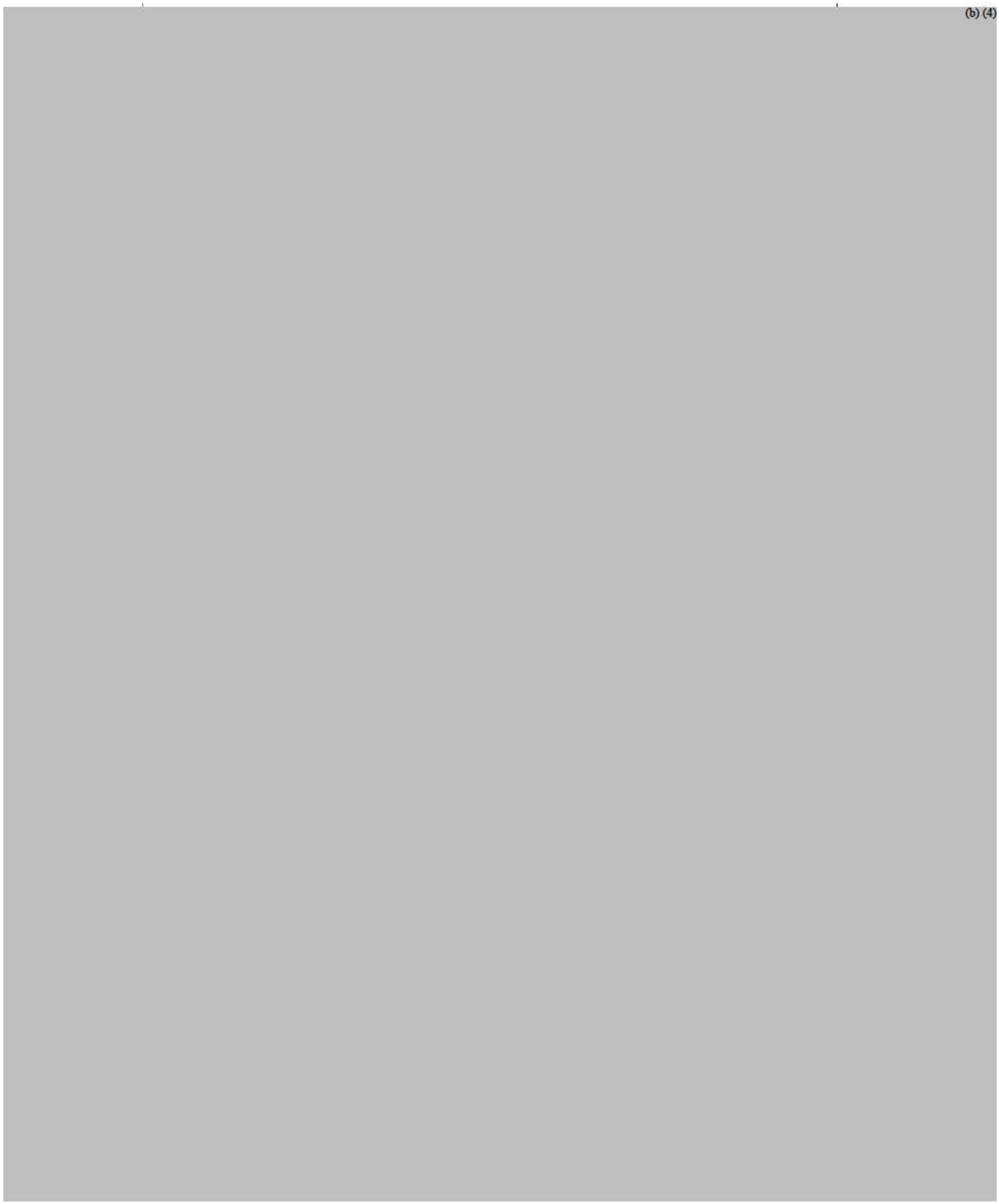
2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Patel M. Label and Labeling MEMORANDUM for Aklief (NDA 211527). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 19. RCM No.: 2018-2153-1.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON AUGUST 30, 2019 AND SEPTEMBER 13, 2019

Container labels



4 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MADHURI R PATEL
10/01/2019 12:18:32 PM

SEVAN H KOLEJIAN
10/01/2019 12:48:05 PM

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	211527
PDUFA Goal Date	October 4, 2019
OSE RCM #	2018-2154
Reviewer Name(s)	Lindsey W. Crist, Pharm.D., BCPS
Team Leader	Donella Fitzgerald, Pharm.D.
Deputy Division Director	Jamie Wilkins, Pharm.D.
Review Completion Date	August 26, 2019
Subject	Evaluation of Need for a REMS
Established Name	Trifarotene
Trade Name	Aklief
Name of Applicant	Galderma Research and Development, LLC
Therapeutic Class	Retinoid acid receptor agonist, topical
Formulation(s)	Topical cream with pump
Dosing Regimen	Apply a thin layer to affected areas once daily in the evening

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Aklief (trifarotene) is necessary to ensure the benefits outweigh its risks. Galderma Research and Development, LLC submitted a New Drug Application (NDA) 211527 for trifarotene with the proposed indication for the topical treatment of acne vulgaris (b) (4) in patients 9 years of age and older. The risks associated with trifarotene are consistent with the class effects of topical retinoids, most commonly local cutaneous reactions such as irritation, pruritis, and sunburn. The Applicant did not submit a proposed REMS or risk management plan with this application.

The Division of Risk Management (DRISK) has determined that a REMS is not needed to ensure the benefits of trifarotene outweigh its risks. The safety concerns associated with trifarotene are well documented and consistent with known class effects of topical retinoids, therefore the prescribers of trifarotene are likely to be aware of the risks, and the risks can be communicated through labeling.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Aklief (trifarotene) is necessary to ensure the benefits outweigh its risks. Galderma Research and Development, LLC (Galderma) submitted a New Drug Application (NDA) 211527 for trifarotene with the proposed indication for the topical treatment of acne vulgaris (b) (4) (b) (4) in patients 9 years of age and older. This application is under review in the Division of Dermatology and Dental Products (DDDP). The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Aklief (trifarotene), a new molecular entity[a], is a retinoid acid receptor (RAR) agonist proposed for the topical treatment of acne vulgaris (b) (4) in patients 9 years of age and older. Topical retinoids treat acne by normalizing follicular hyperkeratosis, preventing the formation of microcomedones, and through anti-inflammatory effects.[1]

Trifarotene is proposed as a 0.005% cream available in 30, 45, and 75-gram pumps. Each gram of the cream contains 50 micrograms of trifarotene. The proposed dosing regimen is to apply a thin layer to the affected areas on the face and/or trunk every evening. Treatment continues until acne lesions improve or resolve but may also continue as maintenance therapy.[b] The topical retinoid agents currently available for acne treatment do not require a REMS program for safe use. Trifarotene is not currently approved in any jurisdiction.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 211527 relevant to this review:

- 10/4/2018: NDA 211527 submission for the topical treatment of acne vulgaris (b) (4) (b) (4) in patients 9 years of age and older received.[2]
- 03/18/2019: A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for trifarotene.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Acne vulgaris (AV) is a common dermatologic disorder in the United States, affecting around 50 million people.[3] AV is considered a disorder of adolescence with about 85% of people 12 to 25 years reporting acne.[4,c] However, acne may persist into adulthood with about 26% of women and 12% of men reporting acne into their forties.[5]

AV is a chronic, inflammatory disease of pilosebaceous follicles that is multifactorial in etiology. Important factors in the formation of acne lesions include increased sebum production, follicular hyperkeratinization, altered immune and inflammatory responses, and colonization of *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*). There are two major types of acne lesions: non-inflammatory (open and closed comedones) and inflammatory (papules, pustules, and in severe cases, nodules/nodulocystic lesions). Microcomedones are the precursor for both lesion types. AV varies in severity according to lesion types, numbers, and extent of involvement.

The clinical course is characterized by remissions and recurrences. AV can result in decreased quality of life and significant psychosocial morbidity including higher rates of depression, anxiety, and low self-worth. Long-term consequences may include permanent scarring and post-inflammatory hyperpigmentation.[4,6,d]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Several topical and systemic drugs are available for the treatment of AV. Guidelines from the American Academy of Dermatology provide an algorithm for selecting treatment options based on severity.[3] Topical therapies such as benzoyl peroxide or retinoids are recommended as first-line options as monotherapy or in combination with other topical or systemic agents depending on acne severity and patient response. Choice of a specific agent depends on patient preference, skin type, and acne distribution. Systemic agents are reserved for severe, recalcitrant, nodulocystic AV. Combination

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

therapy utilizing agents with complementary mechanisms is often required for treatment success.[3,4] See Table 1 in the Appendix, for more details about available acne treatments.

4 Benefit Assessment

The efficacy and safety of trifarotene 0.005% cream for the treatment of acne vulgaris was demonstrated in two pivotal phase 3 studies (Study 18251, NCT02566369 and Study 18252, NCT02556788). A Phase 3 open-label study (Study 18250, NCT02189629) provided additional long-term safety and efficacy evidence.[7]

The two pivotal studies were identical in design: multicenter, randomized, double-blind, parallel-group, and placebo (vehicle)-controlled. The eligibility criteria for both pivotal trials were consistent: moderate[e] facial acne for patients 9 and older and moderate facial and truncal acne for patients 12 and older. The presence of truncal acne was optional for patients 9 to 11 years old. Patients were randomized (1:1) to trifarotene 0.005% cream or a vehicle cream applied daily to the face (and trunk if applicable) for 12 weeks. Both studies had the following co-primary endpoints: success on the Investigator's Global Assessment (IGA)[f], absolute change in facial noninflammatory lesion count, and absolute change in facial inflammatory lesion count at Week 12. The co-secondary endpoints evaluated truncal acne and included success on the Physician's Global Assessment (PGA) Scale, absolute change in truncal noninflammatory lesion count, and absolute change in truncal inflammatory lesion count at Week 12.

The long-term safety and efficacy of trifarotene was evaluated in Study 18250. This was a multicenter, open-label, non-comparative study for up to 52 weeks. Eligibility criteria and efficacy endpoints were similar to the pivotal trials.

Results

The pivotal Phase 3 studies, 18251 and 18252, enrolled a total of 2420 subjects 9 years of age and older. A total of 2206 subjects (91.2%) completed the studies. Trifarotene treatment resulted in statistically significant improvements in the co-primary and co-secondary endpoints compared to the vehicle groups in both studies. Treatment results for the pivotal study co-primary (face) and co-secondary (trunk) endpoints are summarized below in the Table 1 and Table 2.

[e] Defined as Investigator's Global Assessment (IGA) grade 3 and a minimum of 20 inflammatory lesions and 25 non-inflammatory lesions on the face at screening and baseline.

[f] IGA Success Rate defined as the percentage of subjects who achieved an IGA score of 1 (almost clear) or 0 (clear) and at least a 2-grade improvement from baseline to week 12

Table 1. Results for the Co-Primary (Face) Endpoints[6]

	Study 18251			Study 18252		
	Trifarotene N=612	Vehicle N=596	Treatment Effect (p-value)	Trifarotene N=602	Vehicle N=610	Treatment Effect (p-value)
IGA Success (Face)	29.4%	19.5%	9.8% (<0.001)	42.3%	25.7%	16.6% (<0.001)
Inflammatory Lesions						
Baseline Mean	34.7	34.8		36.1	37.0	
Week 12 Mean	15.7	19.3		12.0	17.6	
Change, LS Mean	-19.0	-15.4	-3.6 (<0.001)	-24.2	-18.7	-5.6 (<0.001)
Non-Inflammatory Lesions						
Baseline Mean	54.0	52.8		50.6	51.2	
Week 12 Mean	28.0	34.5		20.6	28.9	
Change, LS Mean	-25.0	-17.9	-7.1 (<0.001)	-30.1	-21.6	-8.5 (<0.001)

Source: Division of Dermatology and Dental Products. Draft Multidisciplinary Review for trifarotene, NDA 211527

Table 2. Results for the Co-Secondary (Trunk) Endpoints[6]

	Study 18251			Study 18252		
	Trifarotene N=600	Vehicle N=585	Treatment Effect (p-value)	Trifarotene N=598	Vehicle N=609	Treatment Effect (p-value)
PGA Success (Trunk)	35.7%	25.0%	10.7% (<0.001)	42.6%	29.9%	12.7% (<0.001)
Inflammatory Lesions						
Baseline Mean	37.5	36.2		39.3	39.1	
Week 12 Mean	15.9	17.9		13.5	18.8	
Change, LS Mean	-21.4	-18.8	-2.5 (<0.001)	-25.5	-19.8	-5.7 (<0.001)
Non-Inflammatory Lesions						
Baseline Mean	47.0	48.3		46.4	45.8	
Week 12 Mean	24.5	29.4		20.5	24.5	
Change, LS Mean	-21.9	-17.8	-4.1 (0.001)	-25.9	-20.8	-5.0 (<0.001)

Source: Division of Dermatology and Dental Products. Draft Multidisciplinary Review for trifarotene, NDA 211527

Long-term efficacy was evaluated in Study 18250 as a secondary endpoint. A total of 455 subjects were enrolled and 348 (76.5%) completed the study. The effectiveness of trifarotene improved over time with IGA success in 65.1% and PGA success in 66.9% of patients, respectively, by Week 52.

The clinical review team concluded that the data from the 2 adequate and well-controlled trials provided substantial evidence of the effectiveness of trifarotene for the treatment of acne vulgaris in the population age 9 years and older.[g,6]

[g] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

5 Risk Assessment & Safe-Use Conditions

The primary safety analysis for trifarotene in acne vulgaris is based on the pooled data from the two pivotal phase 3 trials (Study 18251 and Study 18252). The analysis included subjects who received 12 weeks of trifarotene 0.005% cream (N=1220) or vehicle cream (N=1200) to the face and trunk. Additional safety data was provided from Study 18250, the long-term safety trial, which consisted of 453 subjects treated with trifarotene therapy for 52 weeks.[8,h]

The most common treatment emergent adverse events (TEAEs) related to trifarotene treatment in the primary safety analysis included application site irritation (7.5%, [91/1220]), application site pruritis (2.4%, [29/1220]), and sunburn (2.6%, [32/1220]). Cutaneous reactions were also the most common reported adverse reaction in the long-term trial. Most reactions were mild to moderate and improved over time. Local tolerability adverse events (erythema, dryness, scaling, stinging/burning) were actively assessed by investigators at baseline and at least one follow-up visit. A higher proportion of subjects treated with trifarotene had worsening symptoms of local tolerability from baseline compared to vehicle cream.

Rates of treatment discontinuation were similar between trifarotene (9.6% [117/1220]) compared to vehicle cream (8.1%, [97/1200]) in the pivotal studies. Discontinuation due to adverse events was low overall, however, higher in the trifarotene group (1.9%, [23/1220]) compared to vehicle group (0.2%, [2/1200]). The most common TEAE leading to discontinuation in the trifarotene group was application site irritation. In the long-term safety study, the primary reasons for discontinuation were withdrawal by subject (11.6%, [53/455]) and adverse event (3.5%, [16/455]). All of the TEAEs that led to discontinuation in the long-term study were cutaneous reactions with the exception of 1 event of polycystic ovaries.

5.1 Serious Adverse Events[i,j]

There were no deaths in the studies. In the double-blind safety population, the frequency of treatment-emergent serious adverse events (SAE) was the same in the trifarotene group (6 patients (0.5%) reporting 7 serious TEAEs) and the vehicle cream group (6 patients (0.5%) reporting 7 serious TEAEs).

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[h] Study 18250 enrolled 455 subjects, however, only 453 subjects received treatment and were included in the analysis.

[i] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

[j] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

The 7 SAEs in the trifarotene group included facial bone fracture, ligament sprain, procedural dizziness, cellulitis, infectious mononucleosis, suicide attempt, and major depression. The 7 SAEs in the vehicle group included appendicitis, atypical pneumonia, sinusitis, suicide attempt, hereditary angioedema, urinary tract infection, and asthma. None of the SAEs were considered related to the study drug by the Applicant or clinical reviewer.[6,8]

Twelve SAEs were reported by 10 patients (2.2%) in the long-term safety study. Severe SAEs included nasal septum deviation, acute pyelonephritis, post-procedural hemorrhage following adenotomy, abortion spontaneous, and complex partial seizures. None of the SAEs were considered related to the study drug.[6,8]

5.2 Adverse Events of Special Interest

5.2.1 Embryofetal Toxicity

Systemic exposure to retinoids is associated with embryofetal toxicity. The oral retinoid, isotretinoin, is subject to a REMS to mitigate the risk of embryofetal toxicity. Topical retinoids are not subject to a REMS, however, labeling for the approved topical retinoids communicates the data on teratogenicity in Section 8, Special populations with the exception of tazarotene which is contraindicated in pregnancy (See Table 1 in the Appendix for more detail). There are case reports of embryofetal toxicity in pregnant women exposed to topical retinoids, however, there is not a clear pattern or association. A consult by the Division of Pediatric and Maternal Health (DPMH) summarized that observational studies also do not find increased risk of major malformations or spontaneous abortions with topical retinoids.[9]

In animal reproductive studies, oral trifarotene had teratogenic effects in animals at levels greater than 500 times the maximum recommended human dose.[8] Although the use of a highly effective contraceptive method was required in the clinical studies for trifarotene, 12 pregnancies were reported during the clinical development program (8 on trifarotene and 4 on vehicle) Of the 8 subjects on trifarotene, there were 4 miscarriages, 1 normal delivery, 1 baby with temporary respiratory distress, and 2 lost to follow up. Of the subjects on vehicle, there was 1 miscarriage, 2 normal deliveries, and 1 elective abortion. None of the miscarriages were considered related to study drug. The DPMH reviewer concluded that the data is too limited to make definitive conclusions on the teratogenicity potential for trifarotene.[9] Section 8, Special Populations will summarize the paucity of data for the use of trifarotene in pregnant women.

6 Expected Postmarket Use

Trifarotene is expected to be prescribed by various prescribers including but not limited to primary care physicians, dermatologists, and other specialists involved in the treatment of acne. These prescribers are likely to be familiar with the management of adverse events associated with topical retinoids. Trifarotene is likely to be used by patients in the outpatient setting.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for trifarotene beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The review team recommends approval of trifarotene for the topical treatment of acne vulgaris in patients 9 years of age and older based on the available efficacy and safety information.[6]

Acne vulgaris is the most common dermatological disorder in the US. It is a chronic disease of sebaceous follicles that is multifactorial in etiology. The severity can vary according to lesion types, numbers, and extent of involvement. Acne vulgaris can result in decreased quality of life, psychosocial morbidity, permanent scarring, and post-inflammatory hyperpigmentation. Several topical and systemic products are approved for treatment of acne vulgaris.

The benefit of trifarotene was demonstrated in two phase 3 clinical studies. Trifarotene cream was statistically superior to a vehicle cream in the co-primary endpoints of success on the IGA, absolute change in facial noninflammatory lesion count, and absolute change in facial inflammatory lesion count at Week 12. Co-secondary endpoints evaluating truncal acne were also statistically superior in the trifarotene group compared to the vehicle group.

The safety profile for trifarotene appears similar to other topical retinoids used for treatment of acne vulgaris. The most common adverse reactions were local cutaneous reactions such as site irritation, pruritis, and sunburn. Similar to other topical retinoids, the proposed label includes the potential for local cutaneous reactions and effects of ultraviolet light and environmental exposure in the Warnings and Precaution section. The proposed label also summarizes the limited data on teratogenicity. Adverse event profiles of other topical retinoids are well characterized and do not require a REMS. The clinical reviewer concluded that trifarotene's risks can be communicated with labeling and routine pharmacovigilance.[6]

Therefore, based on the data available, and the prescribing community's familiarity with the risks associated with trifarotene, which do not pose unique REMS considerations compared with the risks associated with other topical retinoid therapies, DRISK is not recommending a REMS for the management of the risks of trifarotene therapy.

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. The safety concerns associated with trifarotene use are well documented and similar to other topical retinoid agents. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

Should DDDP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 References

1. Chien A. Retinoids in Acne Management: Review of Current Understanding, Future Considerations, and Focus on Topical Treatments. *J Drugs Dermatol.* 2018;17(12):s51-55.
2. Galderma. Orig-1 application for trifarotene, NDA 211527. October 4, 2018.
3. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol.* 2016;74(5):945-973.e933.
4. Zaenglein AL. Acne Vulgaris. *N Engl J Med.* 2018;379(14):1343-1352.
5. Collier CN, Harper JC, Cafardi JA, et al. The prevalence of acne in adults 20 years and older. *J Am Acad Dermatol.* 2008;58(1):56-59.
6. Division of Dermatology and Dental Products. DRAFT Multidisciplinary Review and Evaluation for Aklief (trifarotene), NDA 211527 August 14, 2019.
7. Galderma. Summary of Clinical Efficacy for trifarotene, NDA 211527. October 4, 2018.
8. Galderma. Summary of Clinical Safety for trifarotene, NDA 211527. October 4, 2018.
9. Roca C. Division of Pediatric and Maternal Health. Division of Pediatric and Maternal Health Review: Pregnancy and Lactation Labeling for Aklief (trifarotene), NDA 211527. June 13, 2019.
10. Drugs@FDA: FDA Approved Drug Products. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed March 11, 2019.
11. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. https://www.micromedexsolutions.com/ Accessed March 11, 2019.

10.2 Currently Available Treatments for Acne Vulgaris[10,11]

Drug Class	Products	Safety and Tolerability Issues	Risk Management Approaches
Topical Products			
Salicylic acid	Multiple products	Skin irritation, dryness, allergic reactions, avoid eye contact	Labeling - over the counter (OTC) warnings
Benzoyl peroxide	Multiple products	Avoid contact with eyes or mucous membrane, skin irritation, dryness, photosensitivity, allergic reactions	Labeling - OTC warnings
Sulfa products	Sulfacetamide, Sulfur	Hypersensitivity, possible cross-sensitivity with sulfonamides, severe skin reactions	Labeling - OTC warnings
Azelaic acid	Multiple products	Skin irritation (burning, pruritis, stinging), hypopigmentation, exacerbation of asthma (gel), hypersensitivity reactions	Labeling – Warnings and Precautions
Retinoids	Tretinoin	Skin irritation (dryness, pain, erythema, irritation, and exfoliation),	Labeling – Warnings and Precautions

		photosensitivity and risk for sunburn, caution in extremes of weather	
	Adapalene	Ultraviolet light and environmental exposure, skin irritation (erythema, scaling, dryness, and stinging/burning)	Labeling – Warnings and Precautions
	Tazarotene	Embryofetal toxicity	Labeling – Contraindication in pregnancy[b], Warnings and Precautions
		Skin irritation, photosensitivity and risk for sunburn, hypersensitivity, flammable	Labeling – Warnings and Precautions
Antibiotics	Clindamycin	Diarrhea, Clostridium difficile-associated diarrhea (CDAD)	Labeling – Warnings and Precautions
	Erythromycin	Pseudomembranous colitis, skin irritation	Labeling – Warnings and Precautions
	Metronidazole	Carcinogenesis (animal data), peripheral neuropathy, blood dyscrasias), eye irritation - avoid contact with eyes, skin irritation	Labeling – Warnings and Precautions
	Dapsone	Methemoglobinemia, hemolysis associated with G6PD deficiency	Labeling – Warnings and Precautions
Combination products	Various fixed-dose product combinations of benzoyl peroxide, antibiotics, and/or retinoids (safety dependent on individual drug components as described above)		
Systemic products			
Antibiotics	Tetracycline	Teratogenic effects, CDAD, intracranial hypertension/pseudotumor cerebri, photosensitivity	Labeling – Warnings and Precautions
	Doxycycline	Teratogenic effects, CDAD, intracranial hypertension/pseudotumor cerebri, esophagitis/ulcerations, hepatotoxicity photosensitivity, , development of drug resistant bacteria	Labeling – Warnings and Precautions
	Minocycline	Teratogenic effects, photosensitivity, CNS effects, intracranial hypertension/pseudotumor cerebri, superinfection, development of drug resistant bacteria	Labeling – Warnings and Precautions
	Sarecycline	Teratogenic effects, intracranial hypertension, CNS effects (light-headedness, dizziness), CDAD, photosensitivity	Labeling – Warnings and Precautions

Retinoids	Isotretinoin	Teratogenicity	REMS (iPLEDGE Program) – includes medication guide, elements to assure safe use Labeling - Boxed Warning
		Psychiatric disorders, pseudotumor cerebri, serious skin reactions, pancreatitis, elevated triglycerides, hearing impairment, hepatotoxicity, inflammatory bowel disease	Labeling - Warnings and Precautions
Oral contraceptives	Ethinyl estradiol and norgestimate Ethinyl estradiol and norgestimate Ethinyl estradiol and drosperinone	Cigarette smoking and serious cardiovascular events	Labeling – Boxed Warning
		Thromboembolism, liver disease, high blood pressure, gallbladder disease, carbohydrate and lipid metabolic effects, headache, bleeding irregularities and amenorrhea, depression, carcinoma of breast and cervix, increased serum concentration on binding globulins, hereditary angioedema exacerbation, chloasma	Labeling – Warnings and Precautions[c]
Anti-androgen	Spironolactone[a]	Fluid or electrolyte imbalance (hyperkalemia, hypomagnesemia, hyponatremia, hypochloremic alkalosis), gynecomastia, somnolence and dizziness, hypotension and worsening renal function	Labeling – Warnings and Precautions

[a] *Not an FDA-approved indication*

[b] *Systemic exposure is dependent upon the extent of the body surface area treated. In patients treated topically over sufficient body surface area, exposure could be in the same order of magnitude as in orally treated animals.*

[c] *Additional warnings and precautions specific to each product exist*

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/s/

LINDSEY W CRIST
08/26/2019 10:57:17 AM

DONELLA A FITZGERALD
08/26/2019 11:00:51 AM

JAMIE C WILKINS PARKER
08/26/2019 11:25:13 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 19, 2019
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	NDA 211527
Product Name and Strength:	Aklief (trifarotene) cream, 0.005%
Applicant/Sponsor Name:	Galderma Research and Development, LLC
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OSE RCM #:	2018-2153-1
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised professional sample container label received on June 19, 2019 and 30 grams, 40 grams, and 75 grams container labels and carton labeling, Prescribing Information (PI) and Patient Package Insert (PPI) received on August 12, 2019 for Aklief. Division of Dermatology and Dental Products (DDDP) requested that we review the revised container labels, carton labeling, Prescribing Information (PI) and Patient Package Insert (PPI) for Aklief (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

We find the PI and PPI acceptable from a medication error perspective. However, the revised container labels and carton labeling are unacceptable from a medication error perspective. We note the inactive ingredient listing for ethanol is inconsistent with that found in the revised PI and PPI. Additionally, the Aklief 0.005 %, 30 g presentation linear barcode appears to be for printing position.

[a] Patel M. Label and Labeling Review for Aklief (NDA 211527). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 27. RCM No.: 2018-2153.

3 RECOMMENDATIONS FOR GALDERMA RESEARCH AND DEVELOPMENT, LLC

We recommend the following be implemented prior to approval of this NDA:

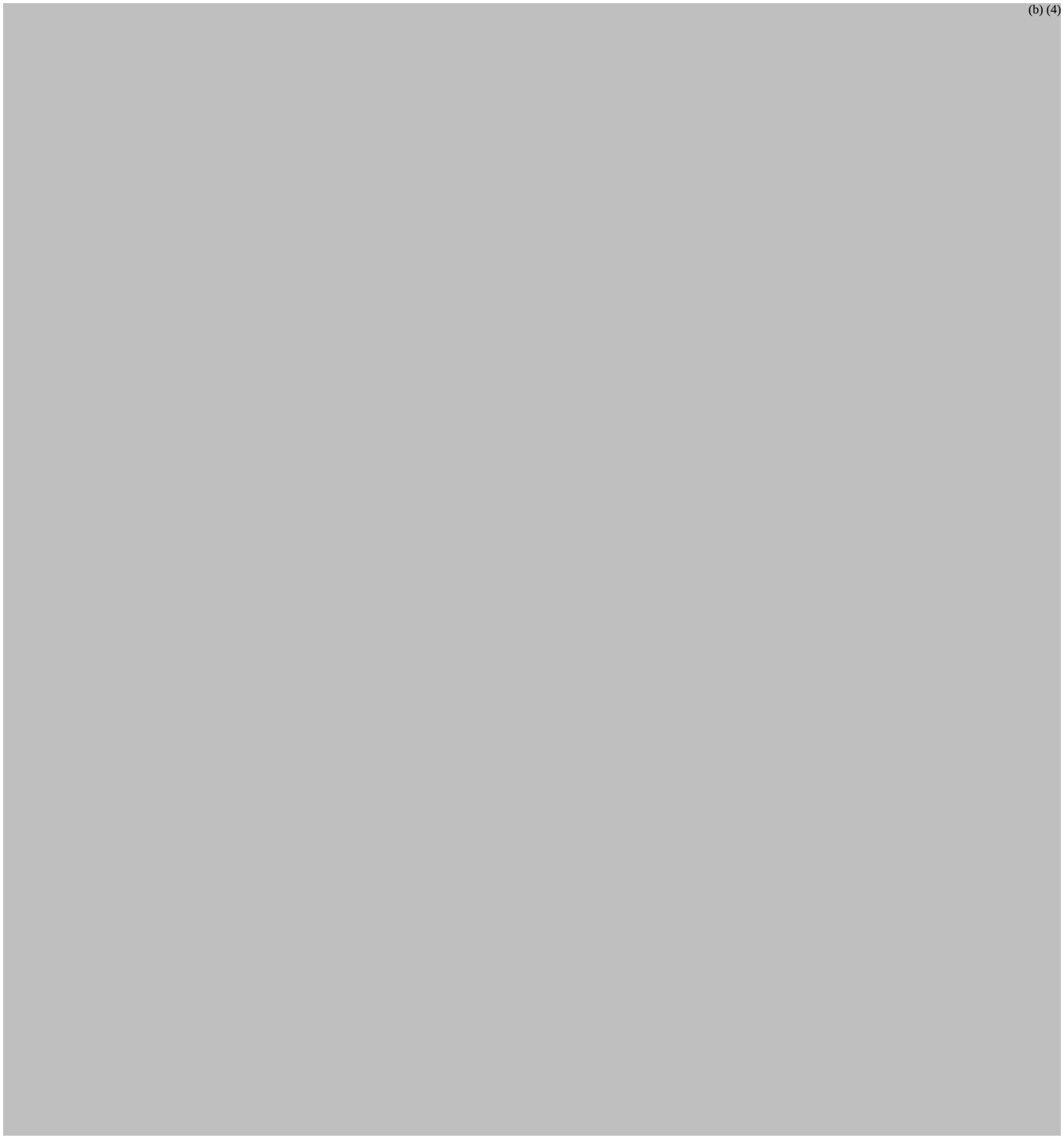
A. Container Labels and Carton Labeling (30 gram pump, 45 gram pump, and 75 gram pump):
   a) We note the inactive ingredient listing for ethanol is inconsistent with that found in the revised PI and PPI. Revise the inactive ingredients information to be consistent throughout all labels and labeling.

B. Container Labels (30 gram Pump):
   a) As currently presented the barcode on the 30 g container label appears to be for printing position only. Please ensure the linear barcode for the 30 g bottle pump label contains, at a minimum, the NDC. The drug barcode is often used as an additional verification before drug administration in the patient care setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product's linear barcode as required per 21CFR 201.25(c)(2).

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JUNE 19, 2019 AND AUGUST 12, 2019

Container labels

(b) (4)



4 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MADHURI R PATEL
08/19/2019 01:59:38 PM

SEVAN H KOLEJIAN
08/19/2019 02:12:16 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatric and Maternal Health Review

Date: 6/13/2019 **Date consulted:** 5/15/2019

From: Catherine Roca, M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

To: Division of Dermatology and Dental Products (DDDP)

Drug: AKLEIF (trifarotene) cream 50 mcg/g

NDA: 211527

Applicant: Galderma Research and Development, LLC

Subject: Pregnancy and Lactation Labeling

Indication: For the topical treatment of acne vulgaris in patients 9 years of age and older

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 211527
- DPMH consult request dated May 15, 2019, DARRTS Reference ID 4433557
- DPMH review of ALTRENO (tretinoin) NDA 209353, Catherine Roca, M.D., May 25, 2018. DARRTS Reference ID 4269131[1]
- DPMH review of SOLAGE (mequinol and tretinoin) Topical Solution 2%/0.01%, Catherine Roca, M.D., January 29, 2019. DARRTS Reference ID 4269131.[2]

[1] The ALTRENO consult review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.
[2]The SOLAGE consult review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.

- OSE Integrated Review of DIFFERIN (adapalene) Gel, 0.1%, Lopa Thambi, PharmD and Hongliu Ding, M.D., Ph.D., March 14, 2016. DARRTS Reference ID 3902112[3]
- FAERS Cases from 2016 OSE Review

Consult Question: "Please provide any recommendations for labeling in response to PLLR conversion."

INTRODUCTION AND BACKGROUND

On October 4, 2018, the applicant, Galderma Research and Development LLC, submitted a New Drug Application (NDA) for a new molecular entity (NME) for AKLIEF (trifarotene) cream 50 mcg/g for the treatment of acne vulgaris in patients 9 years of age and older. DDDP consulted DPMH on May 15, 2019 to assist with the Pregnancy and Lactation subsections of labeling.

AKLEIF (trifarotene) cream 50 mcg/g Drug Characteristics[4]

Drug Class	Trifarotene is a retinoid.
Mechanism of action	Trifarotene has high retinoic acid receptor (RAR) activity and very high selectivity for RAR gamma, the receptor subtype present is in keratinocytes and relevant to acne. Trifarotene modulates retinoid target genes involved in differentiation and inflammatory processes.
Molecular weight	459.58 Daltons
Protein Binding	Approximately 99.9% plasma protein bound
Relevant Inactive Ingredients	AKLIEF contains (b) (4) ethanol.
Half-life	The terminal half-life ranged from 2 to 9 hours.
Absorption	The absorption of trifarotene was evaluated in a study involving 19 adult subjects with acne vulgaris following once daily application of AKLIEF cream for 29 days (daily dose range 1.5 gm/d to 2 gm/day) to the face, shoulders, chest and back. Systemic concentrations were at steady state following 2 weeks of treatment and were quantifiable in 7 subjects. Steady state C_{max} ranged from below the limit of quantification (less than 5 pg/mL) to 10 pg/mL and the $AUC_{0-24\ h}$ ranged from 75 to 104 pg.h/mL in adults.
Serious Adverse Reactions	• Skin irritation: erythema, scaling, dryness, and stinging/burning • Ultraviolet light and environmental exposure: avoid excessive exposure to sunlight, sunlamps, or phototherapy.

REVIEW

Nonclinical Experience

Oral administration of trifarotene to pregnant rats during the period of organogenesis at doses that resulted in systemic exposures greater than 1600 times those in humans at the maximum recommended human dose (MRHD) of AKLIEF Cream resulted in adverse fetal effects, including fetal deaths, reduced mean fetal weight, and external, visceral, and skeletal malformations. Oral administration of trifarotene to pregnant rabbits during the period of

[3] The DIFFERIN OSC Integrated review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.
[4] AKLEIF (trifarotene) proposed package insert

organogenesis at doses that resulted in systemic exposures at least 800 times those in humans at the MRHD of AKLIEF Cream resulted in adverse fetal effects, including defects of the tail, limbs, urogenital organs, and vertebral column.

Trifarotene administered orally to female rats from gestation Day 6 to lactation Day 20, at doses that resulted in systemic exposures up to 594-times those in humans at the MRHD of AKLIEF Cream, had no effect on maternal function or behavior, including gestation, delivery, pup-rearing, lactation and nursing, or survival or development of pups. There were no effects of maternal treatment on behavior, learning, memory, or reproductive function of pups.

The reader is referred to the full Pharmacology/Toxicology review by Norman See, Ph.D., and Barbara Hill, Ph.D.

Reviewer comment:
The exposures in the nonclinical studies that resulted in adverse fetal effects were at multiples greater than 500-times the MRHD of AKLIEF cream.

Review of Pharmacovigilance Database

The applicant reported patients who became pregnant during Phase 3 studies. Of these pregnancies, eight were exposed to trifarotene cream and four were exposed to the vehicle cream. The outcomes of the eight pregnancies were as follows:

- Four miscarriages (all had other risk factors for miscarriage – smoking, obesity, or infection)
- Two normal deliveries (one infant had temporary respiratory distress)
- Two pregnancies lost to follow-up (one of these patients had a normal ultrasound at 6 months gestation)

Complete details are below in the applicant's table below.

Table 35 Pregnancies reported during the trifarotene development program

Study ID	Subject Number	Outcome	Treatment	Duration of exposition to study drug	Relevant concomitant treatment	Risks factors	Gynecological history
RD.03.SRE.40190	(b) (6)	Healthy baby born at 38 weeks	trifarotene cream at 25 µg/g and 100 µg/g (patch test) (+ vehicle and white petroletum)	First 9 days of pregnancy	None	Epilepsy	- One full term birth - One voluntary abortion for personal reason
		Miscarriage (2 weeks after the start of the pregnancy)	trifarotene cream at 25 µg/g and 100 µg/g (patch test) (+ vehicle and white petroletum)	First 2 weeks of pregnancy	None unknown stop date of contraception	Smoking	- One healthy baby - One miscarriage after a 2-month pregnancy
RD.06.SRE.18223		Miscarriage (2 months after the start of pregnancy)	Vehicle Cream applied once daily	First 45 days of pregnancy	- Contraceptive the 45 first days of pregnancy - Antibiotics (amoxicillin and clindamycin) and analgesics for tooth pain	- Polycystic ovary syndrome - Smoking - Severe obesity	None
		Miscarriage (45 days after the start of pregnancy)	trifarotene 25 µg/g cream applied once daily	First 7 days of pregnancy	None	Obesity	One healthy baby
RD.06.SRE.18214		Full Term Delivery Tachypnea (baby) (signs consistent with possible fluid inhalation, resolved in 2 days)	trifarotene 50 µg/g cream (5 days/week)	First 4 weeks of pregnancy	None	Polycystic syndrome	None

Study ID	Subject Number	Outcome	Treatment	Duration of exposition to study drug	Relevant concomitant treatment	Risks factors	Gynecological history
RD.03.SRE.40153E	(b) (6)	Miscarriage (1 month after the start of pregnancy)	- trifarotene 50 µg/g cream A - trifarotene 100 µg/g cream A - Calcipotriol 50 µg/g - betamethasone dipropionate 500 µg/g - vehicle gel	14 days during the second and third weeks of development	Exposed to oral contraception until the discovery of the pregnancy (during 20 days)	Smoking	Two healthy babies
RD.03.SRE.18250		Miscarriage	trifarotene 50 µg/g cream	First week of pregnancy	Clotrimazole for vaginal infection in first week of pregnancy, 4 days before miscarriage amoxicillin / clavulanic acid for tonsillitis 9 days before miscarriage	37 years old	None
RD.03.SRE.18251		Healthy baby	Vehicle Cream applied once daily	First 4 weeks of pregnancy	Levonorgestrel 1.5 mg as emergency contraceptive during the first week of pregnancy flu vaccine during the second quarter of pregnancy	20 years old	None
		Elective abortion	Vehicle Cream applied once daily	First 4 weeks of pregnancy	None	29 years old	None
RD.03.SRE.18252		Unknown (subject lost to follow-up)	trifarotene 50 µg/g cream applied once daily	First three weeks of pregnancy	Singulair® (montekulast sodium) 10 mg for Asthma Proair HFA® (salbutamol sulfate)	23 years old	None
		Healthy baby	Vehicle Cream applied once daily	First trimester of pregnancy	Yadine® (drospirenone and ethinylestradiol)	31 years old	None
RD.03.SRE.103918	(b) (6)	Lost to follow-up (last ultrasound examination performed 6 months prior expected delivery date shown normal female fetus)	trifarotene 50 µg/g cream levonorgesterel / ethinyl estradiol as per protocol	Approximately 13 days	Prenatal vitamins	29 years old	Four previous pregnancies (3 full term normal children living and 1 miscarriage)

HFA= hydrofluoroalkane.

Reviewer comment:
Data on the effects of trifarotene during pregnancy are limited. No congenital malformations were reported in the few pregnancies that were exposed to trifarotene. Miscarriages that occurred during the clinical trials are complicated by other factors that independently increase the risk for miscarriage, such as infection, smoking and obesity.

Review of Literature

Applicant's Review of Literature:
The applicant did not provide a review of the literature related to trifarotene and pregnancy.

DPMH Review of Literature:
DPMH conducted a search of the published literature in PubMed and Embase using the search terms, "trifarotene and pregnancy," "trifarotene and congenital malformations," "trifarotene and stillbirth," and "trifarotene and miscarriage." No papers were located in the search.

DPMH independently considered the literature previously reviewed for the ALTRENO (tretinoin) NDA 209353 consult (see Appendix B) and conducted a limited literature search to capture any new information published since the search conducted for the ALTRENO (tretinoin) NDA 209353[5] DPMH consult using the search terms, "tretinoin and pregnancy," "tretinoin and congenital malformations," "tretinoin and stillbirth," and "tretinoin and miscarriage" from May 2018 through May 2019. The search also was expanded to include the terms, "topical retinoids and pregnancy." One new paper was located in the search that reported 14 cases of pregnancy during six years of post-marketing data on topical alitretinoin for severe chronic hand eczema. The authors state there were no reports of cases of congenital malformations. Most pregnancies were electively terminated (n=8). There were also two spontaneous abortions, one ectopic pregnancy and one healthy infant.[6]

Reviewer comment:
There is no published literature on trifarotene in pregnancy. A review of the published literature by DPMH indicates that larger prospective studies, in general, do not indicate an increased risk of major malformations or spontaneous abortion with topical retinoids. (Oral retinoids are known teratogens.) Systemic absorption of topical retinoids appears to be limited, and exposure of a fetus would be expected to be low. Prospective observational studies do not indicate an increased risk of birth defects or other adverse maternal or fetal effects with topical retinoid exposure. These studies have methodological limitations, including limited sample size and, in some studies, lack of direct examination of the infants by a dysmorphologist. Six cases in the literature report birth defects; however, these case reports do not establish a pattern or association with retinoid-related embryopathy. A recent FDA review of FAERS cases and the published literature by the Division of Pharmacovigilance and the Division of Epidemiology on the effects of topical retinoids in pregnancy similarly did not establish an association with congenital malformations.[7]

LACTATION
Nonclinical Experience
Trifarotene is present in rat milk[8].

The reader is referred to the full Pharmacology/Toxicology review by Norman See, Ph.D., and Barbara Hill, Ph.D.

Review of Pharmacovigilance Database
The applicant reports no cases related to lactation and trifarotene.

Review of Literature
Applicant's Review of Literature:
The applicant did not report a review of the literature related to trifarotene and lactation.

[5] DPMH Review of ALTRENO (tretinoin) NDA 209353, Catherine Roca, M.D., May 25, 2018, DARRTS Reference ID 4269131.
[6] Morris M, et al. Safety of alitretinoin for severe refractory chronic hand eczema: clinical studies and postmarketing surveillance. J Dermatol Treatment. 2016;27(1):54-58.
[7] Pharmacovigilance, epidemiology and drug utilization review by Lopa Thambi Pharm. D. and Hongliu Ding, Ph.D., March 14, 2016 DARRTS Reference ID 3902112.
[8] Applicant's Summary of Clinical Safety - Trifarotene

DPMH Review of Literature:
DPMH conducted a search of *Medications in Mother's Milk,*[9] the Drugs and Lactation Database (LactMed),[10] Micromedex,[11] *Drugs in Pregnancy and Lactation,*[Error! Bookmark not defined.] and of the published literature in PubMed and Embase using the search terms "trifarotene" and "lactation" or "breastfeeding."

No articles on trifarotene were found in the published literature; trifarotene is not referenced in LactMed or Hale.

For a review of topical retinoids and lactation, the reader is referred to the DPMH consult review of ALTRENO (tretinoin) NDA 209353.[12] In summary, no cases of infant exposure during lactation to tretinoin or adapalene were located in the literature. Briggs,[13] Hale[14] and LactMed[15] indicate that topical tretinoin was unlikely to present a significant risk to a breastfed infant.

Reviewer comment:
Data on the safety of topical trifarotene use during breastfeeding are not available; however, systemic absorption is low and infant exposure is expected to be minimal. The applicant recommends that women not apply topical tretinoin to the nipple and areola to avoid direct infant exposure, which is a reasonable precaution.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Nonclinical Experience
Trifarotene was administered to male rats via oral gavage for four weeks prior to mating, during mating and up to termination (approximately 6 weeks in total) and female rats were treated via oral gavage for 2 weeks prior to mating through day 7 of gestation. No adverse effects on fertility or mating were observed at doses approximately 1755 (males) and 1726 (females) times higher than the MRHD of AKLIEF cream.

[9] Hale, Thomas and Rowe, Hilary E. (2017). Medications and Mother's Milk. New York, NY. Springer Publishing.
[10] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.
[11] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 4/23/2018
[12] DPMH review of ALTRENO (tretinoin) NDA 209353, Catherine Roca, M.D., May 25, 2018. DARRTS Reference ID 4269131
[13] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk 10th Ed. 2015. Online, accessed 6/10/2019
[14] Hale, Thomas and Rowe, Hilary E. (2017). Medications and Mother's Milk. New York, NY. Springer Publishing. pp. 949-950.
[15] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

The reader is referred to the full Pharmacology/Toxicology review by Norman See, Ph.D., and Barbara Hill, Ph.D.

Review of Pharmacovigilance Database
The applicant does not report cases related to infertility from the clinical trials.

Review of Literature
Applicant's Review of Literature:
The applicant did not report a review of the literature related to trifarotene and infertility or hormonal contraceptives.

DPMH Review of Literature:
DPMH conducted a review of Micromedex, Embase, and PubMed using the terms, "trifarotene" and "fertility," "contraception," "oral contraceptives," and "infertility."

No papers on the effects of trifarotene on fertility or interactions with hormonal contraceptives were located in the search.

Reviewer comment:
(b) (4)

DISCUSSION AND CONCLUSIONS
Pregnancy
Trifarotene has teratogenic effects in animals at levels > 500 times the MRHD. Data from the applicant's database are limited to eight cases of exposure during pregnancy.

Lactation
Data on the safety of trifarotene during lactation are lacking, but systemic absorption is low and infant exposure is expected to be minimal. DPMH recommends the following language be added to labeling,

> The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AKLIEF and any potential adverse effects on the breastfed infant from the AKLIEF or from the underlying maternal condition.

DPMH agrees with the applicant's proposal to add a Clinical Considerations heading to 8.2, to advise breastfeeding women not to apply AKLIEF directly to the nipple and areola to avoid direct ingestion by the infant.

(b) (4)

Additional Considerations

AKLIEF Cream contains ethanol (b) (4) Published studies have demonstrated that alcohol is associated with fetal harm including central nervous system abnormalities, behavioral disorders, and impaired intellectual development.[16] Based on e-mail communication between May 28 and May 29, 2019 with the DDDP Pharmacology/Toxicology team, the team noted that "The exposure to ethanol with this product would be minimal. As a maximum-exposure scenario, if we assumed approximately 10 grams of AKLIEF might be applied per day, this amount of product would contain approximately 500 mg of ethanol. For comparison, one can of beer (5% ethanol) would contain 17.75 g of ethanol (35 times as much). Plus, ethanol is very poorly absorbed through the skin."[17] Based on the recommendations from the DDDP Pharmacology/Toxicology team, it was decided that adding information on ethanol to the labeling would be confusing and with no benefit to the patient.

LABELING RECOMMENDATIONS

DPMH revised sections 8.1, 8.2, and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from clinical trials with AKLIEF Cream use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are case reports of major birth defects similar to those seen in fetuses exposed to oral retinoids in pregnant women exposed to other topical retinoids, but these case reports do not establish a pattern or association with retinoid-related embryopathy.

In animal reproduction studies, oral doses of trifarotene administered to pregnant rats and rabbits during organogenesis that resulted in systemic exposures more than 800 times the systemic exposure at the maximum recommended human dose (MRHD) of AKLIEF Cream resulted in adverse fetal effects, including fetal deaths and external, visceral, and skeletal malformations *(see Data).*

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4%, respectively.

Data

Animal Data

Oral administration of trifarotene to pregnant rats during the period of organogenesis at doses that resulted in systemic exposure greater than 1600 times those in humans at the MRHD of

[16] https://www.cdc.gov/ncbddd/fasd/facts.html

[17] Email from Norman See, May 29, 2019

AKLIEF Cream resulted in adverse fetal effects, including fetal deaths, reduced mean fetal weight, and external, visceral, and skeletal malformations.

Oral administration of trifarotene to pregnant rabbits during the period of organogenesis at doses that resulted in systemic exposures at least 800 times those in humans at the MRHD of AKLIEF Cream resulted in adverse fetal effects, including defects of the tail, limbs, urogenital organs, and vertebral column.

Trifarotene administered orally to female rats from gestation Day 6 to lactation Day 20, at doses that resulted in systemic exposures up to 594-times those in humans at the MRHD of AKLIEF Cream had no effect on maternal function or behavior, including gestation, delivery, pup-rearing, lactation and nursing, or survival or development of pups. There were no effects of maternal treatment on behavior, learning, memory, or reproductive function of pups.

8.2 Lactation

Risk Summary

There are no data on the prescence of trifarotene in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies, trifarotene was present in rat milk with oral administration of the drug. When a drug is present in animal milk, it is likely that the drug will be present in human milk. It is possible that topcial administration of large amounts of trifarotene could result in sufficient systemic absorption to produce detectable quantities in human milk *(see Clinical Considerations).* The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AKLIEF Cream and any potential adverse effects on the breastfed infant fro AKLIEF Cream or from the underlying maternal condition.

Clinical Considerations

To minimize potential exposure to the breastfed infant via breast milk, use AKLIEF Cream on the smallest area of skin and for the shortest duration possible while breastfeeding. Advise breastfeeding women not to apply AKLIEF Cream directly to the nipple and areola to avoid direct infant exposure.

17 PATIENT COUNSELING INFORMATION

(b) (4)

APPENDIX A – DPMH Review of Literature-Retinoids and Use during Pregnancy

APPEARS THIS WAY ON ORIGINAL

Publication; author/date/ Country	Type of study	Population/control pop.; n	Exposure during pregnancy or pre-conception; to what drug/dose	Pregnancy/infant outcomes	Comments/limitations
Panchaud A[18] 2012 European Network of Teratology Services	Prospective, controlled, multicenter, observational study (11 teratology information services in Europe and Israel)	235 exposed pregnant women; 444 pregnant controls	First trimester exposure (most exposed prior to conception) to topical retinoids, including adapalene (n=24), tretinoin (n=143), isotretinoin (n=52), retinol (n=10), or motretinide (n=1) or combination (n=5)	No significant differences in spontaneous abortion (OR 1.5, (% CI 0.8-2.7), p=0.19; minor birth defects (OR 1.3, 95% CI 0.4-3.7), or major birth defects (OR1.8, 95% CI 0.6-5.4). No cases of retinoid embryopathy. Elective terminations in exposed group were 3 times higher than controls.	No confirmation of birth defects by dysmorphologist
Loureiro KD, et al.[19] 2005 California Teratogen Information Service	Prospective, controlled observational study	106 exposed pregnant women; 389 pregnant controls	First trimester exposure to topical tretinoin	No significant differences between groups (exposed vs control) for spontaneous abortion (6.5% vs 8% p=0.53); major birth defects (2.2% vs 1.2%, p=0.62); or minor birth defects (12.9% vs 9.9%, p=0.51)	Included 62 exposed infants examined by dysmorphologist
Shapiro L, et al.[20] 1997 Motherisk, Canada	Prospective, controlled, observational study	94 exposed pregnant women; 133 pregnant controls	First trimester exposure to topical tretinoin	No difference in spontaneous abortion (p=0.63), elective terminations (p= 0.69), or major birth defects (p=0.30)	Reports by mother and pediatricians, no examination by dysmorphologist
Jick SS, et al.[21] 1993 USA	Retrospective medical/pharmacy records review	215 exposed pregnant women; 430 age-matched pregnant controls	First trimester exposure (defined as obtaining a prescription for topical tretinoin 4 months before and 3 months after conception)	Prevalence of major anomalies in exposed women was 1.9% compared to controls 2.6. RR=0.7, 95% CI 0.2-2.3)	Unclear if prescriptions were taken, concomitant medication/illnesses not reported

[18] Panchaud A, et al. Pregnancy outcome following exposure to topical retinoids: a multicenter, prospective study. J Clin Pharmacol. 2012;52:1844-1851,
[19] Loureriro KD, et al. Minor malformations characteristic of the retinoic acid embryopathy and other birth outcomes in children exposed to topical tretinoin during early pregnancy. Am J Med Genetics 2005;136A:117-121.
[20] Shapiro L, et al. Safety of first-trimester exposure to topical tretinoin: prospective cohort study. Lancet. 1997;350:1143-1144.
[21] Jick SS, et al. First trimester topical tretinoin and congenital disorders. Lancet. 1993;341:1181-1182.

Publication; author/date/ Country	Type of study	Population/control pop.; n	Exposure during pregnancy or pre-conception; to what drug/dose	Pregnancy/infant outcomes	Comments/limitations
Morris M, et al.[22]	Randomized clinical trials and postmarketing surveillance	Two pregnancies occurring during clinical trials and twelve pregnancies from postmarketing reports	Doses not reported; all exposure occurred during the first trimester	• Clinical trials: both pregnancies were terminated (one was an ectopic pregnancy) • Postmarketing reports: -Nine pregnancies electively terminated -Two spontaneous abortions -One healthy infant • There were no reports of congenital malformations reported for any of the pregnancies	Details on the individual cases are lacking, including risk factors for spontaneous abortion such as maternal age, medical conditions, other medications, obstetrical history. Patients treated for hand eczema tend to be older than those treated for acne with an average age of 47.7 years.
Kaplan YC[23] 2015	Systematic review and meta-analysis	Data from four studies with a total of 590 exposed and 1278 unexposed infants (congenital malformation analysis) 430 exposed and 945 unexposed pregnancies (spontaneous abortion) 453 exposed and 874	First trimester	- Congenital malformations (OR 1.22, 95% CI 0.65-2.29) – no studies reported congenital malformations consistent with retinoid embryopathy -Spontaneous abortion (OR 1.02, 95% CI 0.64-1.63) -Stillbirth (OR 2.06, 95% CI 0.43-9.86)	There was no significant heterogeneity between the studies. Rates of elective pregnancy termination were not significantly different between exposed and unexposed groups.

[22] Morris M, et al. Safety of alitretinoin for severe refractory chronic hand eczema: clinical studies and postmarketing surveillance. J Dermatological Treatment. 2016;27(1):54-58.
[23] Kaplan YC, et al. Pregnancy outcomes following first-trimester exposure to topical retinoids: a systematic review and meta-analysis. Br J Dermatol. 2015;173:1132-1141.

Publication; author/date/ Country	Type of study	Population/control pop.; n	Exposure during pregnancy or pre-conception; to what drug/dose	Pregnancy/infant outcomes	Comments/limitations
		unexposed pregnancies (stillbirth)			
Navarre-Belhassen[24] 1998	Case report	Infant born at 40 weeks' gestation	First trimester exposure (gestational months 1 and 2) to topical tretinoin 0.05% and benzoyl peroxide 2.5%, and doxycycline 100 mg bid	Coarctation of the aorta, hypoplastic left hand, hypertelorism, small ear canals	
Lipson AH[25] 1993 Australia	Case report	Female infant (gestational age not reported)	Pre-conception and first trimester (up to week 5 gestation) to topical tretinoin 0.05% with 45% alcohol	Supraumbilical exomphalos, anterior diaphragmatic hernia, inferior pericardial defect, dextroposition of the heart, right sided upper limb reduction defect (hypoplastic scapula and humerus, absence of the radius and ulna, fused fourth and fifth digits and hypoplastic hand	
Selcen D, et al.[26] 2000 USA	Case report	Infant born at 41 weeks' gestation	Prior to conception and first trimester to topical tretinoin 0.025%	Absence of right ear and external auditory canal, cerebral calcification right posterior hemisphere, encephalomalacia right parietooccipital lobe, infarct of basal ganglia	Father also using oral isotretinoin prior to conception
Colley SM, et al.[27] 1998 Australia	Case report	Female infant born at term	Exposure throughout pregnancy to topical tretinoin 0.05%	Cleft lip and palate, fused palpebral fissures, hypertelorism, depressed nasal bridge and deficient left nares, optic tract dysgenesis, arrhinencephalopathy, agenesis of the corpus callosum, fornices, and cingulate gyri and hydrocephalus.	
Camera G and	Case report	Infant born at 41 weeks'	Exposure before conception and up	Hypoplastic ear, atresia of external auditory	

[24] Navarre-Belhassen C, et al. Multiple congenital anomalies associated with topical tretinoin. Ann Pharmacothera. 1998;32(4):505-6.
[25] Lipson AH, et al. Multiple congenital defects associated with maternal use of topical tretinoin. Lancet 1993;341:1352-3.
[26] Selcen D, et al. Otocerebral anomalies with topical tretinoin use. Brain and Development. 2000;22:218-220.
[27] Colley SM, et al. Topical tretinoin and fetal malformations. Med J Australia. 1998;168(9):467.

Publication; author/date/ Country	Type of study	Population/control pop.; n	Exposure during pregnancy or pre-conception; to what drug/dose	Pregnancy/infant outcomes	Comments/limitations
Pregliasco P[28] 1992 Italy		gestation	to 11 weeks' gestation tretinoin 0.05% cream	meatus	
Autret et al.[29] 1997 France	Case report	Termination at 22 weeks	Exposure before conception and up to 13 weeks' gestation adapalene 0.1% gel	Anophthalmia agenesis of the optic chiasma	
Chen C, et al..[30] 1997	Open-label, multiple dose pharmacokinetic study	18 non-pregnant female patients between ages 18-45	42 days of isotretinoin cream 0.1% 0.3 g on 300 cm2 face or 0.15 g on each forearm. Blood samples taken at baseline and day 42	Levels of tretinoin increased by an average of 1.7% at day 42 over the baseline level	

[28] Camera G and Pregniasco P. Ear malformation in baby born to mother using tretinoin cream. Lancet. 1992;339:687.
[29] Autret E, et al. Anophthalmia and agenesis of optic chiasma associated with adapalene gel in early pregnancy. Lancet. 1997;350:339.
[30] Chen C, et al. Negligible systemic absorption of topical isotretinoin cream: implications for teratogenicity. J Clin Pharmacol. 1997;37:279-284.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	June 3, 2019
To:	Kendall Marcus, MD Director **Division of Dermatology and Dental Products (DDDP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Laurie Buonaccorsi, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	AKLIEF (trifarotene)
Dosage Form and Route:	cream
Application Type/Number:	NDA 211527
Applicant:	Galderma Research and Development LLC

1 INTRODUCTION

On October 4, 2018, Galderma Research and Development LLC, submitted for the Agency's review an original New Drug Application (NDA) 211527 for AKLIEF (trifarotene) cream. The proposed indication for AKLIEF (trifarotene) cream is for the topical treatment of Acne vulgaris (b) (4) in patients 9 years of age and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dental Products (DDDP) on February 6, 2019, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for AKLIEF (trifarotene) cream.

2 MATERIAL REVIEWED

- Draft AKLIEF (trifarotene) cream PPI received on October 4, 2018, and received by DMPP and OPDP on May 23, 2019.
- Draft AKLIEF (trifarotene) cream Prescribing Information (PI) received on October 4, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 23, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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LASHAWN M GRIFFITHS
06/04/2019 09:27:12 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 31, 2019

To: Denise Cook/Clinical Reviewer, M.D.
Division of Dermatology and Dental Products (DDDP)

Dawn Williams, Regulatory Project Manager, (DDDP)

Barbara Gould, Regulatory Project Manager, (DDDP)

Nancy Xu, Associate Director for Labeling, (DDDP)

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for AKLIEF® (trifarotene) Cream, for topical use

NDA: 211527

In response to DDDP's consult request dated February 6, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for AKLIEF® (trifarotene) Cream, for topical use (Aklief).

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DDDP on May 23, 2019.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on October 4, 2018, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

AKLIEF CONTAINER/CARTON COMMENTS

1. We recommend that the established name be revised to have prominence commensurate with the proprietary name. The established name should have letters at least half as large as the letters comprising the proprietary name and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features, according to 21 CFR 201.10 (g)(2). The proprietary name is more than twice the size of the established name. Please apply this comment to all attached labels.

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/s/

LAURIE J BUONACCORSI
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Clinical Inspection Summary

Date	18 April 2019
From	Cheryl Grandinetti, Pharm.D. Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Dawn Williams, RPM Denise Cook, M.D., Clinical Reviewer Gordana Diglistic, M.D., Clinical Team Leader Kendall Marcus, MD, Division Director Division of Dermatology and Dental Products
NDA #	211527
Applicant	Galderma Research and Development, Inc
Drug	Trifarotene Cream 50 mcg/g
NME	Yes
Proposed Indication	For the topical treatment of acne vulgaris (b) (4) (b) (4) in patients 9 years of age and older
Consultation Request Date	28 November 2018
Summary Goal Date	18 June 2019
Action Goal Date	18 September 2019
PDUFA Date	4 October 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Coleman, Sanchez, Johnson, and Kemeny were inspected in support of this NDA. Despite minor drug accountability issues at the clinical site of Dr. Coleman and minor discrepancies between the source data and the data listings provided by the sponsor for the primary and secondary efficacy endpoint data that occurred at the clinical sites of Drs. Johnson and Kemeny, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. The final compliance classification of the inspections of Drs. Sanchez and Johnson was No Action Indicated (NAI). The final classification of the inspection of Drs. Coleman and Kemeny was Voluntary Action Indicated (VAI).

II. BACKGROUND

This application was submitted to support the use of trifarotene cream for the treatment of (b) (4) acne vulgaris in patients 9 years of age or older. The key studies supporting this application were the following:

- RD.06.SPR.18251, "A multicenter, randomized, double-blind, parallel-group vehicle-controlled study to compare the efficacy and safety of CD5789 50 mcg/g cream versus vehicle cream in subjects with acne vulgaris"
- RD.06.SPR.18252, "A multicenter, randomized, double-blind, parallel-group vehicle-controlled study to compare the efficacy and safety of CD5789 50 mcg/g cream versus vehicle cream in subjects with acne vulgaris"

Protocol RD.06.SPR.18251:

- *Subjects:* 1524 subjects were screened, 1208 subjects were randomized; 1075 (89.0%) subjects completed the study; 540 subjects (88.2%) in the CD5789 50 mcg/g cream group and 535 (89.8%) subjects in the Vehicle Cream group

- *Sites:* 119 sites in the United States, Canada, Puerto Rico, and Europe

- *Study Initiation and Completion Dates:* First subject enrolled: 30 November 2015; last subject completed: 17 November 2017

Protocol RD.06.SPR.18252:

- *Subjects:* 1293 subjects were screened, 1212 subjects were randomized; 1131 (93.3%) subjects completed the study; 558 subjects (92.7%) in the CD5789 50 mcg/g cream group and 573 (93.9%) subjects in the Vehicle Cream group

- *Sites:* 85 sites in the United States (30 sites), Europe (Hungary, Spain, Czech Republic, Romania, and Poland) (39 sites), Ukraine (8 sites), and Russia (8 sites)

- *Study Initiation and Completion Dates:* First subject screened: 23 Nov 2015; last subject completed: 12 May 2017

These were both multicenter, randomized, double blind, vehicle-controlled studies that compared the efficacy and safety of CD5789 cream to vehicle in pediatric subjects from 9 to <18 years of age and in adults ≥18 years of age with acne vulgaris. The primary objective of the study was to assess the efficacy and safety of CD5789 50 mcg/g cream applied once daily in the evening for 12 weeks in subjects with moderate acne vulgaris.

Clinical trial participation for each subject was approximately 14 weeks. There was a screening period of 14 days with a time window of +3 days followed by 12 weeks of study treatment ±5 days. Subjects who met eligibility criteria were stratified by treatment center and randomized in a 1:1 ratio using an Interactive Response Technology (IRT) System to one the following two treatment groups:

- Group 1: CD5789 50 mcg/g cream applied once daily

- Group 2: Vehicle Cream applied once daily

At the Baseline visit after randomization, a kit number was allocated to the subject by the IRT system. The designated study personnel issued and dispensed one box of study drug with the corresponding kit number at Baseline visit (randomization), Week 4, and Week 8.

The subjects (or caregivers) were instructed to apply a thin layer of the study drug on a daily basis in the evening on the face - chin, left cheek, right cheek, nose and forehead and on the trunk (if applicable)- right and left upper back, right and left shoulders and right and left upper anterior chest reachable to self-application by the subject.

Safety evaluations were performed at Baseline and at Week 1, 2, 4, 8, and 12/Early Termination (ET)/Unscheduled visits. These evaluations consisted of assessment of local tolerability and adverse events at each visit; vital signs and physical examination at Screening, Baseline, and at Weeks 12 /ET/Unscheduled visits; and laboratory tests at Screening and Week 12/ ET.

There were *three co-primary efficacy endpoints*:

- Success rate, defined as the percentage of subjects who achieved an IGA score of 1 (Almost Clear) or 0 (Clear) and at least a 2-grade improvement from Baseline to Week 12. The areas defined for IGA assessment were forehead, each cheek, chin, and nose.
- Absolute change in facial non-inflammatory lesion count from Baseline to Week 12
- Absolute change in facial inflammatory lesion count from Baseline to Week 12

There were *three co-secondary efficacy endpoints*:

- Percentage of subjects who achieved a PGA score of 1 (Almost clear) or 0 (Clear) and at least a 2 grade improvement from Baseline to Week 12
- The areas defined for PGA assessment were shoulders, upper back and upper anterior chest that were accessible to self-application by the subject, i.e., the regions that the subject could easily reach and apply the study drug without assistance
- Absolute change in truncal non-inflammatory lesion count from Baseline to Week 12
- Absolute change in truncal inflammatory lesion count from Baseline to Week 12

IGA and PGA assessments were to be performed by a qualified evaluator and conducted at Screening, Baseline, and at Weeks 1, 2, 4, 8, and 12/ET visits. Evaluators must have completed training prior to performing the IGA and PGA assessments, inflammatory lesion counts (papules and pustules), non-inflammatory lesion counts (open and closed comedones), and other lesion counts (nodules and cysts). Throughout the study, when possible, the same evaluator should have performed the IGA, PGA, and lesion counts for each individual subject. In the event there was a change in the assigned evaluator for a given subject, the reason for change should have been documented. In addition, if it was

not possible to use the same evaluator to follow a given subject, the Sponsor recommended that evaluations between the primary and subsequent evaluator overlap (with both evaluators examining the subject together and the discussing the findings) for at least one visit. This was to be documented in the Source document and in the appropriate Comments section of the eCRF.

Rationale for Site Selection

The clinical sites were chosen primarily based on numbers of enrolled subjects, site efficacy, active complaints for associated INDs, and prior inspectional history.

III. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol #/ # of Subjects Enrolled	Inspection Dates	Classification
Site #8580 Kyle Coleman, MD Etre Cosmetic Dermatology & Laser Center 1224 St. Charles Avenue, Suite C8 New Orleans, LA 70130	RD.06.SPR.18251 Subjects: 20	18 to 20 Mar 2019	VAI
Site #8592 Nestor Sanchez, MD Hospital General Menonita de Aibonito Jose C Vasquez Street Professional Bldg., Suite 304 Albonito, PR 00705	RD.06.SPR.18251 Subjects: 32	25 to 27 February 2019	NAI
Site #8447 Sandy Johnson, MD Johnson Dermatology 5921 Riley Park Dr. 72916 Fort Smith, AR	RD.06.SPR.18252 Subjects: 30	28 to 31 Jan 2019	NAI
Site #5532 Lajos Kemeny, MD University of Szeged Albert Szent-Györgyi Clinical Center Dept of Dermatology and Allergology	RD.06.SPR.18252 Subjects: 55	18 to 22 Feb 2019	VAI

Korànyi Fasor 6-8 H-6720 Szeged, Hungary			

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable

1. Kyle Coleman, M.D.

   At this site, 24 subjects were screened, 20 were enrolled, and 18 completed the study. Records reviewed included, but were not limited to, the study protocol and amendments, Institutional Review Board (IRB) submissions and approvals, subject selection criteria, informed consent, source data, case report forms, source records for the primary efficacy endpoint, financial disclosure, drug accountability, adverse event reporting, protocol deviations, and monitor logs and follow-up letters. An audit of the study records for all 20 enrolled subjects was conducted.

   There was no evidence of under-reporting of adverse events. For all 20 subjects enrolled by this site, the source records for the primary and secondary endpoint data were reviewed and verified against the data listings provided by the sponsor. No discrepancies were noted.

   A Form FDA-483, Inspection Observations, was issued at the end of the inspection for inadequate and inaccurate drug accountability records with respects to dates and quantities dispensed and returned. Specifically, for 6 out of the 20 enrolled subjects, there were 8 entries where the total drug product dispensed and/or returned at a visit as documented on the subject visit worksheet did not correlate with the date and amount dispensed and/or returned as recorded on the site's drug accountability log. Dr. Coleman adequately responded to the inspection findings in a letter dated 22 March 2019.

   Reviewer's comment: The drug accountability discrepancies likely had no impact on the efficacy and safety results of the study as it appears from the records reviewed that all subjects received the correct treatment per their randomization assignment and no drug dispensing errors occurred. The discrepancies appear to be due to inconsistent procedures for processing and documenting subject investigational product receipt and returns.

2. Nestor Sanchez, M.D.

   At this site, 32 subjects were screened, all of whom were enrolled and completed the study. Records reviewed included, but were not limited to, the study protocol and amendments, IRB submissions and approvals, subject selection criteria, informed consent, randomization,

source data, case report forms, source records for the primary efficacy endpoint, financial disclosure, drug accountability, adverse event reporting, protocol deviations, and monitor logs and follow-up letters. An audit of the study records for all 32 enrolled subjects was conducted.

There was no evidence of under-reporting of adverse events. For all 32 subjects enrolled by this site, the source records for the primary and secondary endpoint data were reviewed and verified against the data listings provided by the sponsor. No discrepancies were noted.

Of note, the OSI received a report from the IRB for this site that 9 subjects were consented, re-consented, and/or assented on the English version of the informed consent document instead of the Spanish version, which was the subjects' primary language. During the inspection, the FDA field investigator observed that all 32 participating subjects gave written informed consent prior to enrolling in the study. Although 9 subjects, whose primary language was Spanish, signed an English version of the informed consent, it was noted that these subjects could speak and understand English. Dr. Sanchez stated that English and Spanish are both official languages of Puerto Rico, and English is a required language that is taught to children starting in elementary school.

In addition, in the same report from the IRB, the IRB reported several protocol deviations where subjects had been prescribed exclusionary medications by their personal physicians. During the inspection, the FDA field investigator observed minor protocol deviations for Subject #s (b) (6) involving an insufficient washout period of exclusionary medications, such as amoxicillin, ceftriaxone, vancomycin and prednisolone. The protocol deviations were appropriately documented at the site, and the sponsor reported all of these protocol deviations to the FDA.

3. Sandy Johnson, M.D.

At this site, 32 subjects were screened, 30 were enrolled, and 28 subjects completed the study. Records reviewed included, but were not limited to, the study protocol and amendments, IRB submissions and approvals, subject selection criteria, informed consent, randomization procedures, source data, case report forms, source records for the primary efficacy endpoint, financial disclosure, drug accountability, adverse event reporting, protocol deviations, and monitor logs and follow-up letters. An audit of the study records for all 32 screened subjects was conducted.

There was no evidence of under-reporting of adverse events. For all 30 subjects enrolled by this site, the source records for the primary and secondary endpoint data were reviewed and verified against the data listings provided by the sponsor. One minor discrepancy was noted: for Subject # (b) (6), the number of facial inflammatory lesions for the Week 2 visit (b) (6) was 22 and not 20, as indicated in the data listings provided by the sponsor.

Reviewer's comment: Because the secondary efficacy endpoint involving inflammatory lesion counts is calculated based on the counts at Baseline and Week 12, the data discrepancy noted above likely does not have an impact on the overall efficacy results of the study.

4. Lajos Kemeny, M.D.

   At this site, 55 subjects were screened, all of whom were enrolled, and 53 subjects completed the study. Records reviewed included, but were not limited to, the study protocol and amendments, Ethics Committee submissions and approvals, subject selection criteria, informed consent, randomization, source data, case report forms, source records for the primary efficacy endpoint, financial disclosure, drug accountability, adverse event reporting, protocol deviations, and monitor logs and follow-up letters. An audit of the study records for 20 of the 55 screened subjects was conducted.

   There was no evidence of under-reporting of adverse events. For all 55 subjects enrolled by this site, the source records for the primary and secondary endpoint data were reviewed and verified against the data listings provided by the sponsor. A Form FDA-483, Inspection Observations, was issued at the end of the inspection for failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation. Dr. Kemeny adequately responded to the inspection findings in a letter dated 4 March 2019.

   The following data discrepancies involving the primary and secondary efficacy endpoints were noted.:

Subject #/Randomization	Endpoint variable	Week/Date	Source Data Value	Sponsor Data Listing Value
(b) (6) / CD5789 50 mcg/g	IGA	Week 12/14 Feb 2017	Missing source data	2
(b) (6) / CD5789 50 mcg/g	PGA	Week 12/14 Feb 2017	Missing source data	2
(b) (6) /Vehicle	IGA	Week 4/11 Jan 2017	2	3
(b) (6) /Vehicle	PGA	Week 4/11 Jan 2017	2	3
(b) (6) /Vehicle	PGA	Week 2/3 Jan 2017	2	3
(b) (6) / Vehicle	Facial Inflammatory lesion count	Week 2/9 Jan 2017	21	16

Reviewer's comment: Because the primary and secondary efficacy endpoints are assessed or calculated based on the values at Baseline and Week 12, the data discrepancies noted above for Subject #s (b) (6) likely do not have an impact on the overall efficacy results of the study. Of note, for Subject # (b) (6) IGA and PGA scores at Week 12 could not be verified because source documents were missing at the site. Although we were

unable to verify the accuracy of this data, the Week 12 IGA and PGA scores for a single subject are very unlikely to have a significant impact on the efficacy results of the study.

{See appended electronic signature page}
Cheryl Grandinetti, Pharm.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D. Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
Central Doc. Rm. NDA 211527
DDDP/Project Manager/Dawn Williams
DDDP/Medical Officer/Denise Cook
DDDP/Clinical Team Leader/Gordana Diglistic
DDDP/Division Director/Kendall Marcus
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Cheryl Grandinetti
OSI/ GCP Program Analysts/Yolanda Patague
OSI/Database Project Manager/Dana Walters

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 27, 2019
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	NDA 211527
Product Name and Strength:	Aklief (trifarotene) (b) (4)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Galderma Research and Development, LLC
FDA Received Date:	October 4, 2018
OSE RCM #:	2018-2153
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 REASON FOR REVIEW

The Division of Dermatology and Dental Products (DDDP) requested that we review the proposed container labels, carton labeling, Prescribing Information (PI) and Patient Package Insert (PPI) for Aklief (trifarotene) lotion (NDA 211527), submitted (b) (4) on October 4, 2018, to determine if they are acceptable from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the PI, PPI, container labels, and carton labeling for Aklief. We noted that the strength presentation on container labels and carton labeling (b) (6) which differ from the product strength presentation in the PI (50 mcg/g) and the PPI (50 µg/g). Expressing the product strength in a manner that is incongruent with the dosage and administration of the product complicates the calculating of dosage and has led to dosing errors. We have informed the Division of Product Quality (OPQ) via email communication dated January 16, 2019 and February 21,2019 and we defer to OPQ to determine the appropriate strength presentation for this product.

We also noted that the Prescribing Information can be improved to clarify the package type descriptor. Additionally, the container labels and carton labeling can be improved to enhance the readability and prominence of important information (e.g. established name) and facilitate identification of the product.

4 CONCLUSION & RECOMMENDATIONS

We note the label and labeling can be improved to clarify the package type descriptor and to ensure consistency in the strength presentation. The container labels and carton labeling can be improved to enhance important information and facilitate identification of the product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. General Comments:
The container labels and carton labeling notes the product strength (b) (6) whereas the Prescribing Information (PI) lists the strength as 50 mcg/g, and the Patient Package Insert (PPI) lists the strength as 50 µg/g. Expressing the product strength in a manner that is incongruent with the dosage and administration of the product complicates the calculating of dosage and has led to dosing errors. We have informed Division of Product Quality (OPQ) via email communication dated January 16, 2019 and February 21,2019 about the strength presentation inconsistency and we defer to OPQ to determine the appropriate strength presentation for this product. Ensure that the strength presentation is consistent on all labels and labeling.

B. Prescribing Information

1. How Supplied/Storage and Handling Section

   a. We note the package type descriptor in the How Supplied section of the Prescribing Information is listed as "pump". We note this may be clarified further to prevent confusion with non-topical pumps (i.e. infusion pumps). Additionally, we recommend that the package type descriptor is consistent on all labels and labeling.

4.2 RECOMMENDATIONS FOR GALDERMA RESEARCH AND DEVELOPMENT, LLC

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. The established name should be at least half the size of the proprietary name. Revise the established name to be in accordance with 21 CFR 201.10(g)(2).
2. The established name should be more prominent then the "Rx Only" statement. Decrease the prominence of the statement "Rx Only" on the principal display panel (see Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 [line 146-151]).
3. Identify the expiration date format you intend to use. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. We recommend that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a

year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. We recommend that a hyphen or a space be used to separate the portions of the expiration date. (See *Draft Guidance: Product Identifiers Under the Drug Supply Chain Security Act-Questions and Answers*, September 2018 (lines 277-283), for further insight into FDAs current thinking (found at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf).

B. Container Labels

1. As currently presented, there is no linear barcode on the 30 g bottle pump label. The drug barcode is often used as an additional verification before drug administration in the patient care setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product's linear barcode to each individual tube or bottle pump as required per 21CFR 201.25(c)(2).

C. Carton Labeling

1. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[a] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

[a] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Aklief received on October 4, 2018 from Galderma Research and Development, LLC.

Table 2. Relevant Product Information for Aklief	
Initial Approval Date	N/A
Active Ingredient	trifarotene
Indication	topical treatment of acne vulgaris (b) (6) in patients 9 years of age and older
Route of Administration	topical
Dosage Form	(b) (6)
Strength	(b) (6)
Dose and Frequency	Apply a thin layer to the affected areas (b) (4) in the evening, on clean and dry skin.
How Supplied	(b) (6) 30 gram pump, 45 g pump, and 75 gram pump
Storage	(b) (6)
Container Closure	(b) (6) pump

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Aklief labels and labeling submitted by Galderma Research and Development, LLC.

- Container Labels received on October 4, 2018
- Carton Labeling received on October 4, 2018
- Professional Sample Container Label received on October 4, 2018
- Professional Sample Carton Labeling received on October 4, 2018
- Patient Package Insert (Image not shown) received on October 4, 2018
- Prescribing Information (Image not shown) received on October 4, 2018

G.2 Label and Labeling Images

Container Labels and Professional Sample Container Label

(b) (4)

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

5 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MADHURI R PATEL
03/27/2019 02:30:53 PM

SEVAN H KOLEJIAN
03/27/2019 03:00:06 PM